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Perineural Invasion by Ductal Adenocarcinoma of the Pancreas

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Background and Objectives: The correlation between various levels of perineural invasion by pancreatic carcinoma and the patient's prognosis has never been cleared. The authors carried out a histopathologic study of resected pancreatic carcinoma to elucidate the significance of a new histologic finding concerning perineural invasion, which we designated ''intrapancreatic, extratumoral perineural invasion (*nex*),'' and also to determine its predictive value for prognoses of patients after surgical removal of the tumor.

Methods: We investigated 90 patients with pancreatic adenocarcinoma who had undergone pancreatic resection. The prognoses of all patients were explored, and correlations between survival and pathologic factors were statistically examined for neural invasion.

Results: *Nex* was found in more than 50% of resected pancreases. A statistically significant association was found between the presence of *nex* and the grade of intrapancreatic neural invasion or the presence of extrapancreatic neural plexus invasion. *Nex* was also found to be associated with patient survival after removal of the tumor.

Conclusions: *Nex* appears to be an element predicting pancreatic cancer infiltration to the extrapancreatic nerve plexus and also to be a factor influencing postoperative survival of patients with pancreatic carcinoma.

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KEY WORDS: **pancreatic cancer; histopathology; perineural invasion; survival**

INTRODUCTION

Perineural invasion is widely accepted to be a unique route for the spread of pancreatic carcinoma. Infiltration of its malignant cells to the retroperitoneal nerve plexus through perineural space is one of the major causes of recurrence of curatively resected pancreatic carcinoma. Many investigators have reported the histopathologic characteristics and significance in surgery of neural invasion by ductal adenocarcinoma of the pancreas [1–9]. However, it has never been fully clarified whether there is any correlation between the neural invasion in the pancreatic parenchyma and that in the retroperitoneal nerve plexus. In our previous report [10], we demonstrated the importance of a new histopathologic finding, designated ''intrapancreatic, extratumoral perineural invasion (*nex*)'' as an indicator of retroperitoneal nerve plexus involvement by pancreatic carcinoma. In this study, we reviewed the histopathologic findings of a further 90 patients who had undergone resection of pancreatic carcinoma and proved the dependability of *nex* as a clinicopathologic factor influencing patient survival after removal of the tumor.

MATERIALS AND METHODS

We examined 90 consecutive cases of resection of pancreatic ductal adenocarcinoma, excluding islet cell carcinoma, acinar cell carcinoma, and mucinous cystadenocarcinoma, from the files of the Department of Sur-

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gery, Hokkaido University Hospital, from 1981 to 1995. These cases consisted of 60 (66.7%) men and 30 (33.3%) women. Their ages ranged from 31 to 78 years, with a mean of 60.5 years. Operative procedures consisted of pancreatoduodenectomy in 54, total pancreatectomy in 18, and distal pancreatectomy in 18 cases. Retroperitoneal tissues, including the neural plexus around the superior mesenteric artery, common hepatic artery, and the aorta, were also dissected with regional lymph nodes in all these operations. Resected pancreatic tissues were fixed in 10% formalin and cut vertically along the main pancreatic duct at intervals of 5 mm. Each case was histologically examined and classified by histologic type, tumor size, location, intrapancreatic infiltration to lymph vessels, nodal status, and the following three kinds of neural involvement: intrapancreatic neural invasion (*ne*), retroperitoneal nerve plexus invasion (*pl*), and *nex*. Lymph vessel invasion was designated *ly*1 (slight), *ly*2 (moderate), and *ly*3 (extensive) according to the extent. Neural involvement was evaluated according to the following criteria.

Extrapancreatic Neural Plexus Invasion (*pl*)

All histologic sections, including those from lymph nodes, the choledochus, and blood vessels resected with the pancreas, were inspected to detect extrapancreatic neural plexus invasion. Those with infiltration to one or more extrapancreatic neural plexuses were designated *pl*(+). Those in which involvement by malignant cells was limited to periplexus connective tissues and in which no carcinoma cells were detected within the neural plexus or its perineural space were excluded from *pl*(+).

Intrapancreatic Neural Invasion (*ne*)

The *ne* grades were defined by the numbers of neural fascicles invaded by carcinoma cells in the most extensively involved areas, as observed under low-power magnification (×100). Those with the number of involved fascicles ranging from 1 to 5 were classified *ne*1; from 6 to 9, *ne*2, and over 10, *ne*3. For those with no neural fascicle invasion in a representative section, all their pertinent histologic sections were reviewed. Those with no invaded nerve in any section were classified *ne*0, and those with few invaded nerves in other sections were classified *ne*1.

Intrapancreatic, Extratumoral Perineural Invasion (*nex*)

The perineural invasion evident outside the major tumor mass within the pancreas was designated ''intrapancreatic, extratumoral perineural invasion (*nex*).'' In this category, there was a cancer-free area histologically between the major tumor mass and a *nex*(+) neural fascicle, and no proliferation of carcinoma cells was demonstrated around the *nex*(+) fascicles. In other words, in *nex*(+) cases, one or more perineural invasions were observed in the not directly invaded neural fascicles within the pancreas, regardless of the distance from the major tumor mass. An example of a *nex*(+) neural fascicle is presented in Figure 1. In cancer-free tissue around the *nex*(+) neural fascicle, pancreatic acini, as shown in Figure 1, fibrous tissue of chronic inflammation, or intrapancreatic adipose lobules were usually present. The concept of *nex*(+) was introduced under the hypothesis that *nex*(+) represents a minimal metastasis of tumor cells along a neural route remaining within the pancreas.

To determine correlations among the histological factors, statistical analyses were carried out by the two-tailed chi-square test. $P < 0.05$ was considered significant.

Follow-up periods averaged 18 months (ranging from 1 to 123 months); 97% of the follow-up was either through the Hokkaido University Hospital Registry or by direct contact with the patients. Survival curves were drawn using Kaplan–Meier analysis, and prognostic variables were determined using the log-rank test. Statistically significant differences were accepted at the 5% level.

RESULTS

Results from the analyses of patients' data are as follows.

Histologic Type, Tumor Size, Location, Lymph Vessel Infiltration, Nodal Status, and *pl*(+)

All 90 cases were of duct cell origin. As shown in Table I, they were papillary adenocarcinoma (5), well-differentiated tubular adenocarcinoma (17), moderately differentiated tubular adenocarcinoma (56), poorly differentiated adenocarcinoma (9), and undifferentiated carcinoma (3). The tumors were classified into four groups by maximum diameter: <2 cm (7), 2–4 cm (47), 4–6 cm (25), and >6 cm (11). Tumor sites were the head of the pancreas (69) and the body or tail of the pancreas (21). Lymph vessel invasion was detected in 89 cases (98.9%). In only 1 case, was no lymph vessel invasion seen in any histologic section, designated *ly*0 (Table I). Seventy-six cases (84.4%) had lymph node metastases. Cancer cell invasion of the retroperitoneal connective tissue adjacent to the pancreas, including the neural plexus, was microscopically observed in 79 cases (87.8%).

Forty-seven cases (52.2%) were *pl*(+). The histologic classification did not indicate the presence of retroperitoneal neural plexus invasion. The tumors were classified into four groups according to maximum diameter: <2 cm, 2–4 cm, 4–6 cm, and >6 cm. Two of the seven tumors <2 cm in diameter, 23 of the 47 tumors 2–4 cm, 14 of the 25 tumors 4–6 cm, and 8 of the 11 tumors >6 cm were *pl*(+). Thirty-four (49.3%) of 69 carcinomas in the head of the pancreas and 13 (61.9%) of 21 carcinomas in the body

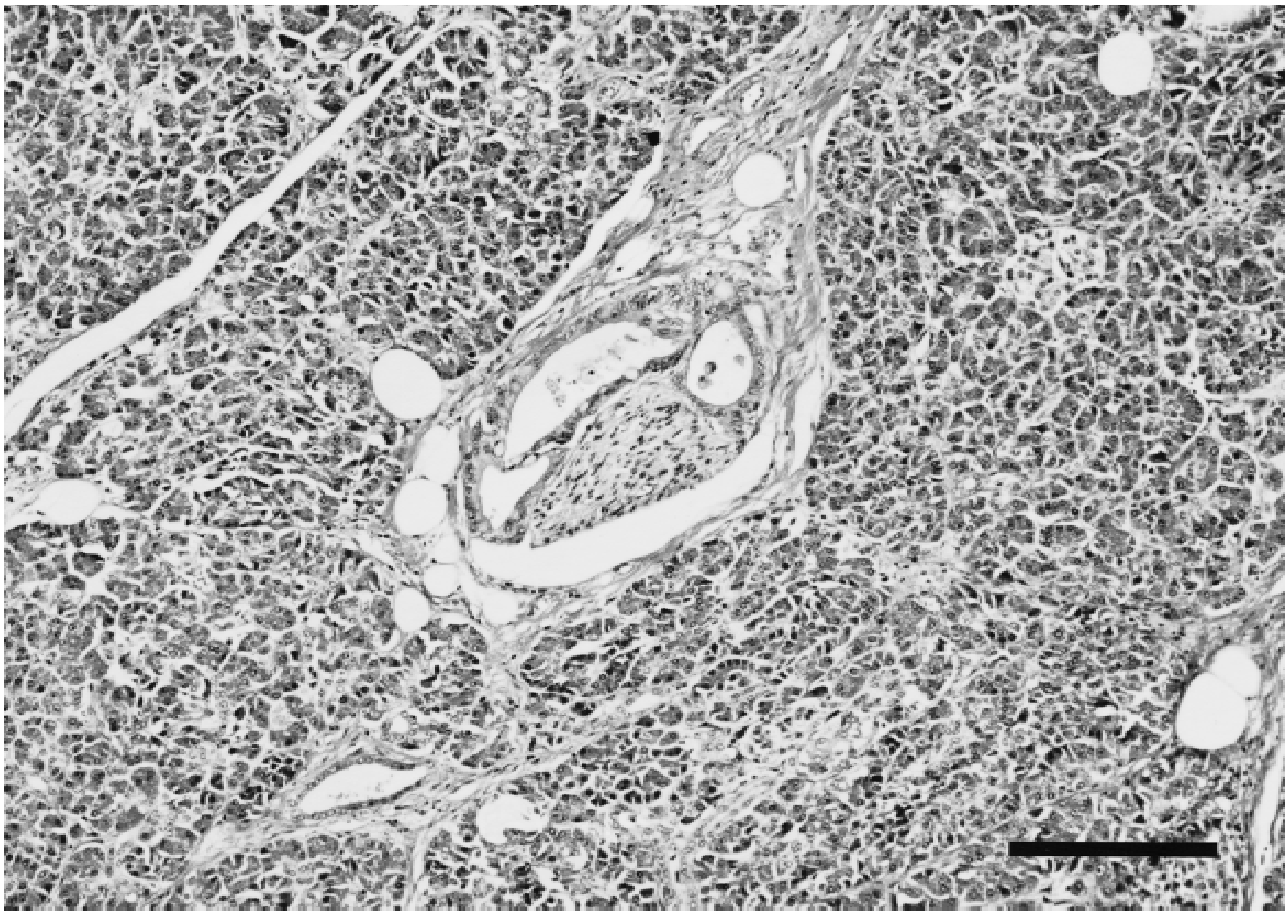

Fig. 1. Representative histologic appearance of intrapancreatic, extratumoral perineural invasion (*nex*). Well-differentiated neoplastic gland in the perineural space of a neural fascicle within the pancreas, but outside the spread of the major tumor mass. Note the lack of malignant cells in the surrounding pancreatic tissue. Bar = 200 μm.

and tail were *pl*(+). Neither the tumor size nor the location correlated with *pl*. Retroperitoneal neural plexus involvement was found in 16 of 34 *ly*1, 22 of 37 *ly*2, and 9 of 18 *ly*3 cases, respectively, but not in the 1 *ly*0 case. Thus, no statistically significant association was noticed between the degree of *ly* and *pl*(+). However, retroperitoneal nerve plexus invasion was detected in two (14.3%) of 14 cases with no lymph node metastases and in 45 (59.2%) of 76 cases with nodal involvement. Only between the presence of nodal metastases and retroperitoneal plexus involvement was a statistically significant association found ($P = 0.0027$).

ne, nex and *pl*

Intrapancreatic neural invasion, *ne*, was found in 88 (97.8%) of the 90 cases: *ne*1 (51), *ne*2 (23), and *ne*3 (14). Intrapancreatic, extratumoral perineural invasion, *nex*(+), was detected in 47 cases (52.2%): *ne*1 (23), *ne*2 (13), and *ne*3 (11) (Table II). There was no statistically significant association between the degree of *ne* and the presence of *nex*. By contrast, *ne* was detected in all 47 *pl*(+) cases: *ne*1 (17), *ne*2 (18), and *ne*3 (12) (Table III). Therefore, there was a statistically significant association between the degree of *ne* and *pl*(+) ($P < 0.0001$). Furthermore, 37 (78.7%) of the 47 *pl*(+) cases were *nex*(+) (Table IV). In *nex*(−) cases, invasion of the extrapancreatic neural plexus was observed only in 10 cases. Therefore, a statistically significant association was evident between *pl*(+) and *nex*(+) ($P < 0.0001$). Sixteen of 17 *pl*-positive *ne*1 cases were *nex*(+). In *ne*1 cases with minimal intrapancreatic neural invasion, 33.3% (17 of 51) were *pl*(+), whereas in *ne*1 and *nex*(+) cases, 69.6% (16 of 23) were *pl*(+). Statistical significance was found between these two figures ($P < 0.0001$) (Table V).

ne, nex, and *pl* in Terms of Survival Periods

There were five postoperative deaths among the 90 patients, with an overall hospital mortality rate of 5.6%. Six late deaths occurred more than 1,000 days after surgery. The cause of death was recurrence of pancreatic carcinoma in five patients. The remaining case, a 72-year-old woman, died of old age without evidence of recurrence at 1,454 days after surgery. The mean survival time after surgery was 2,192 days for the 2 *ne*0 patients,

TABLE I. Extrapancreatic Nerve Plexus Invasion and Other Clinicopathologic Factors of Pancreatic Adenocarcinoma

	pl(+)	*pl*(−)	*P*
Histologic type of adenocarcinoma			
pap	0	5	NS*
well	8	9	
mod	34	22	
por	3	6	
und	2	1	
Tumor size			
≧2 cm	2	5	NS*
<2 cm, ≧4 cm	23	24	
<4 cm, ≧6 cm	14	11	
<6 cm	8	3	
Site			
Head	34	35	NS*
Body or tail	13	8	
Lymph vessel invasion			
*ly*0	0	1	NS*
*ly*1	16	18	
*ly*2	22	15	
*ly*3	9	9	
Lymph node metastasis			
(−)	2	12	0.0027*
(+)	45	31	

*Chi-square test.
pap, papillary; well, well-differentiated; mod, moderately differentiated; por, poorly differentiated; und, undifferentiated carcinoma; NS, nonsignificant.

TABLE II. Correlation Between Grade of Intrapancreatic Neural Invasion (*ne*) and Presence of Intrapancreatic, Extratumoral Perineural Invasion (*nex*) by Pancreatic Adenocarcinoma

Extent of intrapancreatic neural invasion		*nex*(+)		*nex*(−)	
Type	No. of cases	Case	%	Case	%
*ne*0	2	0	0[a]	2	100[a]
*ne*1	51	23	45.1[b]	28	54.9[b]
*ne*2	23	13	56.5[c]	10	43.5[c]
*ne*3	14	11	78.6[d]	3	21.4[d]
Total	90	47	52.2[e,*]	43	47.9[e]

[a]% of 2 *ne*0 cases.
[b]% of 51 *ne*1 cases.
[c]% of 23 *ne*2 cases.
[d]% of 14 *ne*3 cases.
[e]% of all 90 cases.
*$P = 0.063$ by chi-square test.

TABLE III. Correlation Between Grade of Intrapancreatic Neural Invasion (*ne*) and Presence of Extrapancreatic Plexus Invasion (*pl*) by Pancreatic Carcinoma

Extent of intrapancreatic neural invasion		*pl*(+)		*pl*(−)	
Type	No. of cases	Case	%	Case	%
*ne*0	2	0	0[a]	2	100[a]
*ne*1	51	17	33.3[b]	34	66.7[b]
*ne*2	23	18	78.3[c]	5	21.7[c]
*ne*3	14	12	85.7[d]	2	14.3[d]
Total	90	47	52.2[e,*]	43	47.8[e]

[a]% of 2 *ne*0 cases.
[b]% of 51 *ne*1 cases.
[c]% of 23 *ne*2 cases.
[d]% of 14 *ne*3 cases.
[e]% of all 90 cases.
*$P < 0.0001$ by chi-square test.

TABLE IV. Correlation Between Intrapancreatic, Extratumoral Perineural Invasion (*nex*), and Extrapancreatic Plexus Invasion (*pl*)

Intrapancreatic, extratumoral perineural invasion		*pl*(+)		*pl*(−)	
Type	No. of cases	Case	%	Case	%
nex(+)	47	37	78.7[a]	10	21.3[a]
nex(−)	43	10	23.3[b]	33	76.7[b]
Total	90	47	52.2[c,*]	43	47.3[c]

[a]% of 47 *nex*(+) cases.
[b]% of 43 *nex*(−) cases.
[c]% of all 90 cases.
*$P < 0.0001$ by chi-square test.

TABLE V. Correlation Between Intrapancreatic, Extratumoral Perineural Invasion (*nex*) and Extrapancreatic Neural Plexus Invasion (*pl*) in *ne*1 Cases

Intrapancreatic, extratumoral perineural invasion		*pl*(+)		*pl*(−)	
Type	No. of cases	Case	%	Case	%
nex(+)	23	16	69.6[a]	7	30.4[a]
nex(−)	28	1	3.6[b]	27	96.4[b]
Total	51	17	33.3[c,*]	34	67.7[c]

[a]% of 23 *nex*(+) cases.
[b]% of 28 *nex*(−) cases.
[c]% of 51 *ne*1 cases.
*$P < 0.0001$ by chi-square test.

whereas it was 812 days for *ne*1 patients, 338 days for *ne*2 patients, and 247 days for *ne*3 patients. A statistically significant correlation was found between the degree of *ne* and postoperative survival by the log-rank test ($P = 0.0029$) (Fig. 2). The mean survival time after surgery was 1,042 days for the 43 *nex*(−) patients; and it was 350 days for the 47 *nex*(+) patients. There was a statistically significant difference between survival curves of these two groups by the log-rank test ($P = 0.0080$) (Fig. 3). Thus, the postoperative mean survival time of the patients with a low *ne* degree or *nex*(−) was longer than that of those with a high *ne* degree or *nex*(+). The mean survival time of the patients with *pl*(−) was 901 days and that of those with *pl*(+) was 361 days. However, no significant difference was noted between the two groups.

DISCUSSION

Intrapancreatic neural invasion is one of the histopathologic characteristics of pancreas carcinoma. Adenocar-

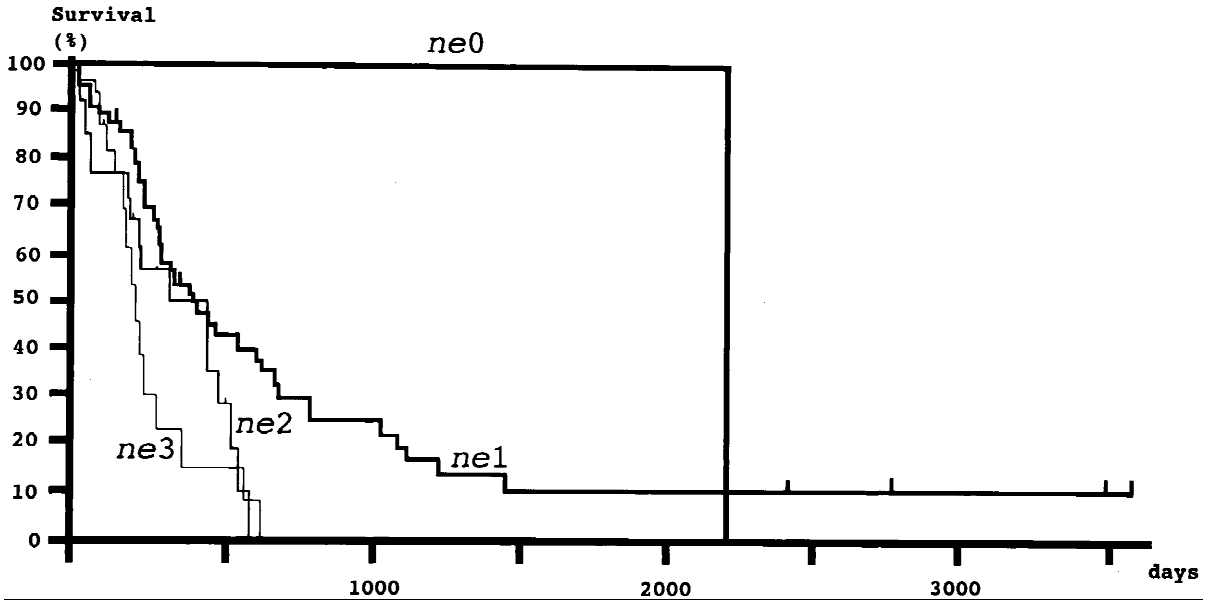

Fig. 2. Cumulative survival curves according to the extent of intrapancreatic neural invasion (*ne*) by Kaplan–Meier analysis. A significant difference was found between the extent of *ne* and the long-term survival by the log-rank test ($P = 0.0029$).

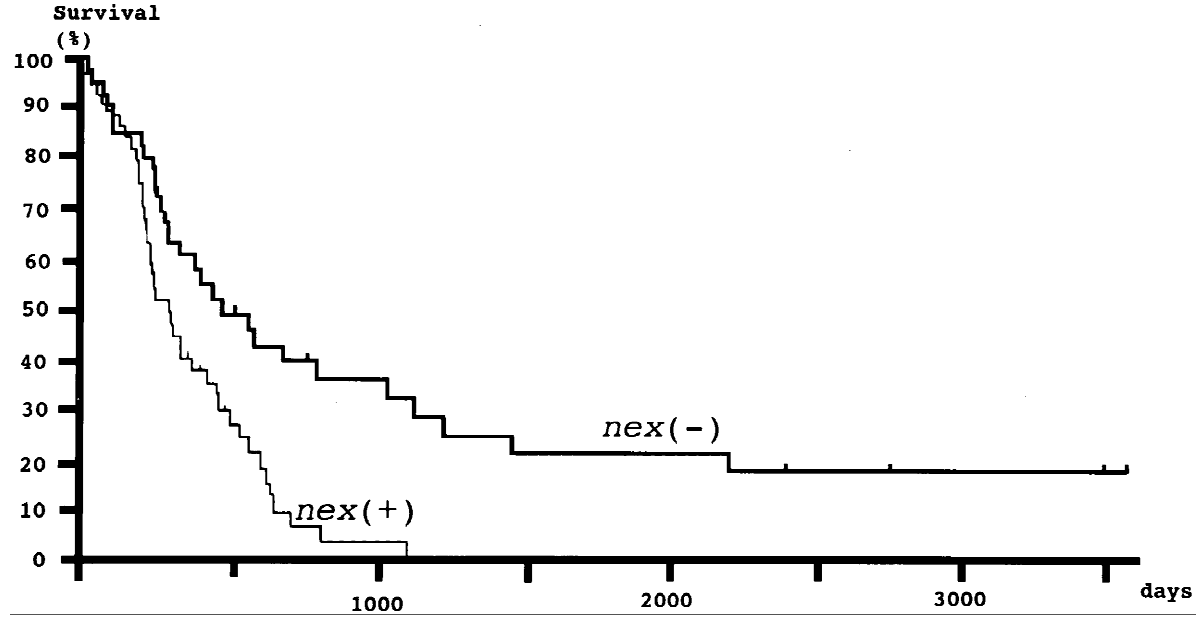

Fig. 3. Cumulative survival curves according to the presence of intrapancreatic, extratumoral perineural invasion (*nex*) by Kaplan–Meier analysis. There was a statistically significant difference between the long-term survival of *nex*(−) cases and *nex*(+) cases by the log-rank test ($P = 0.0080$).

cinoma cells originating from the pancreatic duct epithelium can easily break into the perineural space of intrapancreatic nerve fascicles, as reported by several investigators [11–14]. This perineural involvement by pancreatic cancer cells usually spreads into the retroperitoneal tissue adjacent to the pancreas. In previous reports, retroperitoneal nerve plexus invasion by pancreatic carcinoma was found in about 60% of excised specimens and in 75% of autopsy materials of even small tumors [15]. In our study, it was found in 50% of the materials. In view of such high incidences of infiltration of the retroperitoneal plexus by cancer cells, removal of peripancreatic, retroperitoneal tissue with the pancreas seems to be necessary in curative surgery for almost all patients with pancreatic carcinoma.

The question of whether the route for serial progression of cancer metastasis from the intrapancreatic nerve fascicles to the extrapancreatic plexus via perineural

space is distinct from other routes such as lymphatic or venous canals, has been studied and it is commonly considered today that the perineural space is an independent route for cancer infiltration, since this space is anatomically or ultrastructurally different from the lymphatic canals [16–18]. Nagakawa et al. [12], reported that there was no correlation as a whole between extrapancreatic nerve plexus invasion and lymph node metastasis, although the invasion of the extrapancreatic nerve plexus was marked in cases with extensive lymph vessel invasion. We found statistical significance between *pl* and the presence of lymph node metastasis, but not between *pl* and the degree of lymph vessel invasion. Moreover, we did not recognize any correlation between *pl* and other factors, such as histologic type, tumor size, and site of the tumor. Therefore, we supposed that these histologic findings could not be predictive of retroperitoneal nerve plexus involvement by pancreatic cancer cells.

It was stated in a few clinicopathologic studies [12,19] that the grade of intrapancreatic neural invasion was proportional to the number of incidences of extrapancreatic nerve plexus invasion. In our study, we also recognized a statistically significant relationship between the degree of *ne* and the presence of extrapancreatic perineural infiltration by pancreatic carcinoma. However, we assume that a high degree of intrapancreatic neural invasion does not necessarily indicate infiltration into the extrapancreatic nerve plexus because infiltration into extrapancreatic nerve fascicles was not observed in all those cases with a high extent of intrapancreatic neural invasion. In fact, *pl* was absent in about 20% of *ne*2 or *ne*3 cases in this study as in another report [12]. These facts suggest that there may be another factor in the tendency of cancer to spread toward retroperitoneal tissue through the perineural space. We presume that *nex* might be a representative histological factor in the tendency of the carcinoma cells to invade the extrapancreatic neural plexus. A high incidence of retroperitoneal nerve plexus involvement can be expected in cases demonstrating a high degree of intrapancreatic neural invasion. However, the pathological significance of *nex* was clear in the cases with a low degree of intrapancreatic neural invasion. For instance, even in the *ne*1 group, there were a marked number of *pl*-positive and *nex*-positive cases, as compared with *nex*-negative cases.

In several articles, histopathological findings such as tumor size [1,3,5,20,21], pathological type [3,4], presence or absence of lymph node metastasis [1,3–5,9,22], portal vein system involvement [3,5,23], pancreatic capsular invasion [5,24], and retroperitoneal invasion [24] have been indicated as long-term prognostic factors for patients with pancreatic carcinoma. *pl*(+) is one of the representative indicators of retroperitoneal tissue involvement by pancreatic ductal adenocarcinoma. However, histological factors concerning neural invasion, such as *ne* or *pl*, have never been proved in previous reports to be predictors after removal of the tumor. This may be because of the ambiguity in judging the degree of perineural invasion. In this study, we graded the extent of intrapancreatic neural invasion by the number of nerve fascicles infiltrated by cancer cells, from *ne*0 to *ne*3, to evaluate the degree of intrapancreatic neural invasion. Consequently, the *ne* degree revealed a statistically significant correlation with prognosis after surgery. In addition, this study elucidated that the presence of *nex* was closely related to survival after resection of the tumor. Although there was no statistical significance between *pl* and long-term results after surgery, the significance of *pl* as a clinicopathological factor may be evident if *pl* is graded as *ne*. Moreover, there is a possibility that retroperitoneal plexus invasion is not exclusively caused by progressive infiltration through perineural space in some cases. Since the presence or absence of *pl* had a significant correlation with nodal status, as we demonstrated, the retroperitoneal nerve plexus might be involved by cancer invasion from the nearby lymph node metastases. This would be a reason that *pl* was not valuable as a prognostic factor concerning neural invasion such as *ne* or *nex*.

Previously we substantiated that *nex* could be an indicator for the presence of retroperitoneal neural plexus invasion by pancreas carcinoma in our histological study of 65 resected pancreatic cancer specimens [10]. In the present study, we confirmed our previous results and conclude that *nex* could also be a reliable indicator for survival after resection of pancreatic ductal adenocarcinoma.

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